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CORRESPONDENCE

Fluoroquinolones: are they essential to treat multidrug-resistant tuberculosis?

To the Editors:

We read with interest the excellent letter by HOLTZ and CEGIELSKI [1] contributing to the current discussion on extensively drug-resistant (XDR)-tuberculosis (TB). Several publications have already demonstrated that resistance to fluoroquinolones (FQ) is independently associated with poor outcome and/or that the possibility of including FQ in regimens improves treatment outcomes of multidrug-resistant (MDR)-TB cases [2–4]. This happened before the (recent) description of XDR-TB [1, 5]. We do not know how many of the patients with MDR-TB strains were, in fact, infected with XDR *Mycobacterium tuberculosis*.

We wanted to establish the role of the different XDR-defining components (*e.g.* isoniazid and rifampicin, FQ and injectable second-line drugs) in determining poor treatment outcomes.

Our group has shown for the first time that XDR-TB cases in Italy and Germany have a five-fold increase in the risk of death (relative risk (RR) 5.45; 95% confidence interval (CI) 1.95–15.27; $p<0.01$), require longer hospitalisation than MDR-TB cases (241.2 ± 177.0 *versus* 99.1 ± 85.9 days; $p<0.001$), have a longer treatment duration (30.3 ± 29.4 versus 15.0 ± 23.8 months; $p<0.05$) and, for the few cases who converted, need a longer time to smear/culture conversion ($p<0.01$) [6]. The findings of a second study, which included additional cases from Estonia and the Russian Federation, demonstrated that XDR-TB cases had an RR of 1.58 to achieve death or failure compared with MDR-TB cases resistant to all first-line drugs (95% CI 1.14–2.20; $p<0.05$) and an RR of 2.61 (95% CI 1.45–4.69; $p<0.001$) compared with MDR-TB cases in which susceptibility to at least one first-line drug still existed [7]. These data support the observation that the loss of first-line drugs different from rifampicin and isoniazid has a role in worsening prognosis of MDR-TB cases.

In order to better understand the role of FQ in determining poor treatment outcomes in MDR-TB cases, we re-analysed data from the four-country study [7] to assess whether there is any difference in death or mortality in MDR-TB cases resistant or susceptible to FQ. The overall sample included 425 MDR-TB cases (361 MDR, 64 XDR). A total of 87 (20%) were resistant to FQ, 23 (26%) being MDR and 64 (74%) XDR. Although the proportion of MDR-TB cases resistant to FQ was similar in the three countries reporting FQ resistance (*i.e.* 18, 24 and 24% in Italy, Germany and Estonia, respectively), the proportion of XDR-TB cases among FQ-resistant cases was largely different (50, 27 and 88% in Italy, Germany and Estonia, respectively). FQ-resistant MDR-TB cases yielded a higher proportion of deaths than non-FQ-resistant cases (20 *versus* 12%; $p=0.020$), as well as a higher proportion of treatment failures (19 *versus* 9%; $p=0.038$; table 1).

TABLE 1 Risk of death and failure in fluoroquinolone (FQ)-resistant *versus* FQ-susceptible multidrug-resistant tuberculosis cases from Estonia, Germany, Italy and the Russian Federation among cases achieving a final outcome (treatment success, death and failure)

	FQ-resistant	FQ-susceptible	Univariate analysis	
			RR (95% CI)	p-value
Subjects n	87	338		
Treatment success	30 (34)	157 (46)		
Death#	17 (20)	40 (12)	1.86 (1.11–3.11)	0.020
Failure#	13 (15)	31 (9)	1.84 (1.05–3.23)	0.038

Data are presented as n (%), unless otherwise indicated. Cases not achieving a final outcome (default, still on treatment) were excluded from the analysis. RR: relative risk; CI: confidence interval. #: comparison of treatment success and treatment failure/death between FQ-resistant and FQ-susceptible multidrug-resistant tuberculosis cases.

At the multiple regression analysis, the presence of XDR-TB is the only independent risk factor for both death (odds ratio (OR) 2.07; 95% CI 1.05–4.05; $p<0.034$) and failure (OR 2.37; 95% CI 1.14–4.89; $p<0.02$). The findings of our analysis suggest that FQ contribute to increase the risk of death and failure, being a key XDR-defining variable.

In conclusion, apart from linezolid, fluoroquinolones represent the only ''new'' class of active drugs currently available to treat drug-resistant tuberculosis. They are effective and relatively well tolerated. Furthermore, fluoroquinolones have the potential to allow a reduction in the (still long) short-course chemotherapy regimens. Unfortunately, rapid selection of drug resistance mutants to fluoroquinolones is a well-known phenomenon. Prevention of development of further drug resistance is imperative until new drugs become available in the treatment arena.

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STATEMENT OF INTEREST

None declared.

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Concomitant use of β-blockers and β_2-agonists

To the Editors:

Historically, the use of β-adrenergic blockers in patients with airways disease has been discouraged. However, recent meta-analyses suggest that cardioselective β-blockers are safe in people with mild-to-moderate airways disease [1, 2]. We have identified patients with chest disease on β-agonist bronchodilators, who were simultaneously taking β-blocker drugs. We have also looked at the reasons for co-prescription of these ''competing'' drugs and whether cardioselective β-blockers were being used.

Over 2 yrs (2005–2006) in a district general hospital, C.D. Shee prospectively recorded the names of patients he saw who were concomitantly taking β-blockers and β_2-agonists. Patients were encountered in outpatient clinics, as hospital in-patients and as referrals (consults). The data were analysed retrospectively. A total of 34 patients were identified and hospital notes were found for 27 (18 males, mean (range) age 69 (54–88) yrs). It seemed that the co-prescription of these drugs was often inadvertent. In no instance did the hospital notes nor the general practitioners' letter specifically mention why two competing drug classes were being used simultaneously. It was not always clear whether it was a general practitioner (family doctor) or a hospital doctor who had originally instigated specific drugs.

Of the patients using β-agonists, 19 had diagnoses of chronic obstructive airways disease and eight had asthma. A total of 21 (78%) subjects were taking salbutamol *via* a metered-dose inhaler, four (15%) were taking nebulised salbutamol and two (7%) were taking a long-acting bronchodilator. Cardioselective β-blockers were being taken by 18 (67%) subjects (atenolol n=14, bisoprolol n=3, metoprolol n=1) and nine (33%) subjects were taking nonselective β-blockers (carvedilol n=3, sotalol n=2, propanolol n=2, oxprenolol n=1, carvedilol with sotalol n=1). Eight (30%) subjects were taking β-blockers primarily for heart failure, eight (30%) for isolated hypertension and five (19%) for hypertension with ischaemic heart disease. Other indications were for angina (two subjects), atrial fibrillation (one subject), migraine (one subject), hyperthyroidism (one subject) and unclear (one subject).

In a separate study, on a 1-day in-patient survey (November 21, 2006), drug charts were analysed for 198 patients identified on eight medical wards. Of these, 32 (16%) subjects were taking